Conduction System

Introduction

If you've been paying attention and have done the lessons in order, a lot of this lesson may feel redundant. It feels that way because it is. You saw much of this in General Physiology when we discussed action potentials and skeletal muscle. We'll discuss the familiar voltage-gated channels, action potential, action potential propagation, and conduction velocity, but in a different way. The heart is two syncytia—an atrial syncytium and a ventricular syncytium. Depolarization is carried through gap junctions that connect the cardiac myocytes of each syncytium.

Pacemaker myocytes (from now on, pacemakers) **exhibit automaticity**—they will depolarize after time passes. They can initiate a syncytium's depolarization. In this lesson, we explore what makes a pacemaker a pacemaker and how pacemakers' pace can be controlled by the autonomics (we did that in General Pharmacology from the perspective of the autonomic nervous system, but will tell the story again from the perspective of the heart). **Nonpacemaker myocytes** are the contractile myocytes. The major distinctions between pacemakers and nonpacemakers are their **ion channels** and their **action potential shape**. Most of this lesson is about that.

The atria depolarize and contract as one unit. The ventricles depolarize and contract as one unit. The atria and ventricles do not depolarize or contract at the same time. There is time for the atrial contraction to empty the atria of blood into the ventricles, just before the ventricular contraction occurs. This is because of the AV node, which has reduced conduction velocity. The same channels that give pacemakers their strange action potential also limit the conduction velocity through nodal tissue. The AV node is a cluster of only pacemakers, whereas the syncytia are vastly myocytes with only a few pacemakers throughout.

Channels You Know + Others

Voltage-gated sodium channels, which we simply called **Sodium Channels** (capital S and C) in General Physiology, are the same in cardiac myocytes as they were for action potentials of neurons. They have a resting state (activation gate closed, inactivation gate open), an open state (both gates open), and an inactive state (inactivation gate closed, activation gate open). They open and close **quickly**. While open, the conductance to sodium is very high, sodium rushes into the cells, and the membrane rapidly approaches the equilibrium potential for sodium (very positive, don't learn the numbers). These channels are on **nonpacemaker myocytes**. They account for the rapid conduction velocity, how the signal moves so far and fast throughout the syncytium. Moving from the inactivated state to the resting state requires both time and repolarization. Pacemakers do not have them.

Voltage-gated calcium channels, which we simply called **Calcium Channels** (capital Cs) in General Physiology, are the same L-type voltage calcium channels in cardiac myocytes. Their relationship to the sarcoplasmic reticulum and calcium release is different in cardiac myocytes (RyR2 rather than the mechanoreceptor RyR1), but the transmembrane protein on the cardiac myocytes plasma membrane is the same transmembrane protein on the skeletal muscle cardiac myocyte. We're not discussing myocardial work, calcium conductance, or calcium-dependent calcium release because we are talking about action potentials and not the force of contraction. Calcium Channels are **slower to open** and **slower to close** but have a much lower membrane conductance to calcium than Sodium Channels do to sodium. Calcium also has a depolarizing equilibrium potential. These channels have an activation gate and inactivation gate, just like Sodium channels. Moving from the inactivated state to the resting state requires both time and repolarization. Both pacemakers and nonpacemakers utilize Calcium Channels. The difference between them is discussed below.

Voltage-gated potassium channels, which we simply called **Potassium Channels** (capital P and C) in General Physiology, are the same as we saw in the action potential in axons. Potassium Channels open when depolarized and close when repolarized—there is no inactivation gate. It is the failsafe mechanism that ensures that the only channel that could remain on is one that hyperpolarizes.

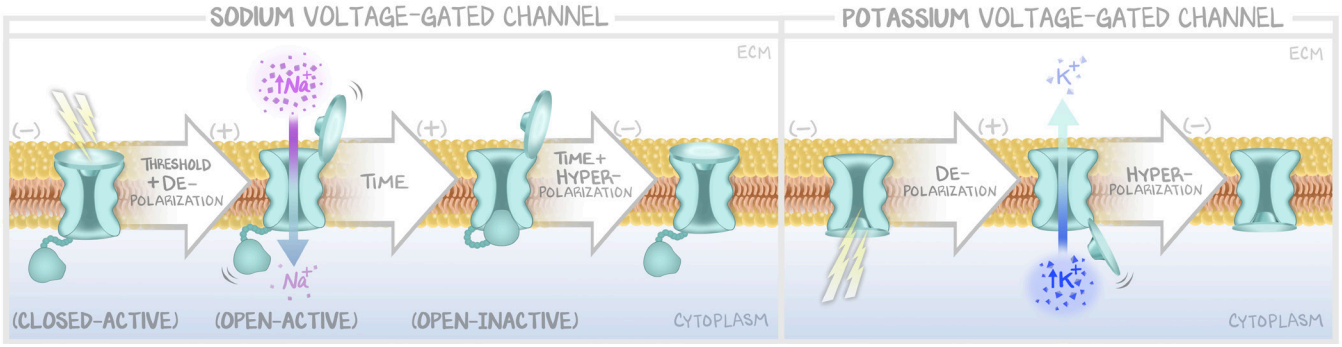

Figure 2.1: Voltage-Gated Channels
Sodium Channels and Calcium Channels follow a similar cycle, but Sodium Channels open faster and close sooner. The sequence is set off by depolarization. The gates remain open for a certain duration before inactivating. Once inactivated, only repolarization and the passage of time will return them to the resting state. Potassium Channels have no inactivation gate and simply open with depolarization and close with hyperpolarization.

Potassium channels that act as **leak channels** are always open, they are few in number, and they keep excitable cells close to the equilibrium pressure of potassium. In cardiac muscle, it is –90 mV (do remember this number).

Channels You Don't Know

This is the first time in our curriculum that you are expected to have encountered the **Funny Channel** with its **Funny Current**. The channel was called Funny and has been recently renamed to something more accurate, but because it is difficult to say, most now call it the **HCN Channel** and the **HCN current**. Both are acceptable, and we're going to call it the Funny Channel. Funny Channels are **nonselective cation channels**. They are always open. They are permeable to both sodium and potassium, much like the nicotinic acetylcholine receptors on skeletal muscle. The average of the equilibrium potentials for Na^+ and K^+ is still a depolarizing stimulus. These channels **enable pacemaker automaticity**. This gets complicated, so we're introducing the channel and the current here with its significance. Its mechanism is discussed below. **Nonpacemakers do not have Funny Channels**.

I_{TO} Channels are important but also annoying. They are also potassium channels and are present only on nonpacemaker myocytes. They open fast and close fast, just like Sodium Channels. These give the cardiac nonpacemaker myocyte action potential its shape. But it isn't a target for treating arrhythmia, nor is it known to cause disease. We are obligated to discuss it, but we really want you to think, "Potassium Channels, Sodium Channels, Calcium Channels, and Funny Channels." I_{TO} Channels (written that way without explanation on purpose) don't fit that mold.

Syncytium and Conduction Velocity

The heart is composed of **two syncytia**: the **atrial** syncytium, which constitutes the walls of the two atria, and the **ventricular** syncytium, which constitutes the walls of the two ventricles. The atria are separated from the ventricles by **fibrous tissue** that surrounds the atrioventricular valvular openings between the atria and the ventricles.

A **conduction velocity** is how fast and how far an electrical signal propagates. An electrical signal decays over space and time. A bigger signal will last longer and be able to travel farther. When there is a depolarization in any one myocyte, because all myocytes are connected through intercalated discs, the ion changes in that first myocyte are felt by nearby myocytes. A small depolarization will decay sooner, will not reach as far as a large depolarization. The **larger the depolarization**, the greater the membrane voltage change, the more positive ion influx, the **further that depolarization** propagates another depolarization in a resting myocyte. The larger the depolarization, the **faster the signal travels**. In contrast, when there is a small depolarization in one myocyte, the influx of ions and the magnitude of the signal will not reach as far as the large depolarization.

The atrial syncytium and the ventricular syncytium are mostly nonpacemaker myocytes. They are like many other excitable cells (General Physiology #7: *Excitable Cells Active Properties*) and have **voltage-gated sodium channels**. These sodium channels, when they open, massively increase membrane conductance to sodium. Like in skeletal muscle, their depolarization is huge. A huge depolarization is communicated to more myocytes, farther away, which propagate that signal by depolarizing, opening their voltage-gated sodium channels, and so on. Nonpacemaker myocytes exhibit **really fast conduction velocity**. That means the syncytia have a really fast conduction velocity.

All pacemakers exhibit automaticity—they will depolarize on their own eventually. In a normal heart, the SA node is the pacemaker of the heart because the SA node's intrinsic automaticity is faster than all the others. The AV node can demonstrate automaticity and be the pacemaker for the heart. In a normal heart, the AV node's purpose is to delay the depolarization from the SA node from entering the ventricular conduction system. This is to give time for the atria to contract and eject—the atrial kick. The AV node has the **slowest conduction velocity** of any place in the heart. The signal moves through the AV node slowly. That means there must be cells with weak depolarization. That means there can be no voltage-gated sodium channels present on nonpacemakers. The AV node is a cluster of **only pacemaker myocytes**. Pacemakers have **no Sodium Channels**, only **Calcium Channels**. Calcium channels cause a **weak depolarization**. Because there are no myocytes with Sodium Channels, the depolarization stimulus is the weakest. The fewest nearby pacemakers depolarize with each nearby depolarization. The signal is moving through the AV node, just slowly.

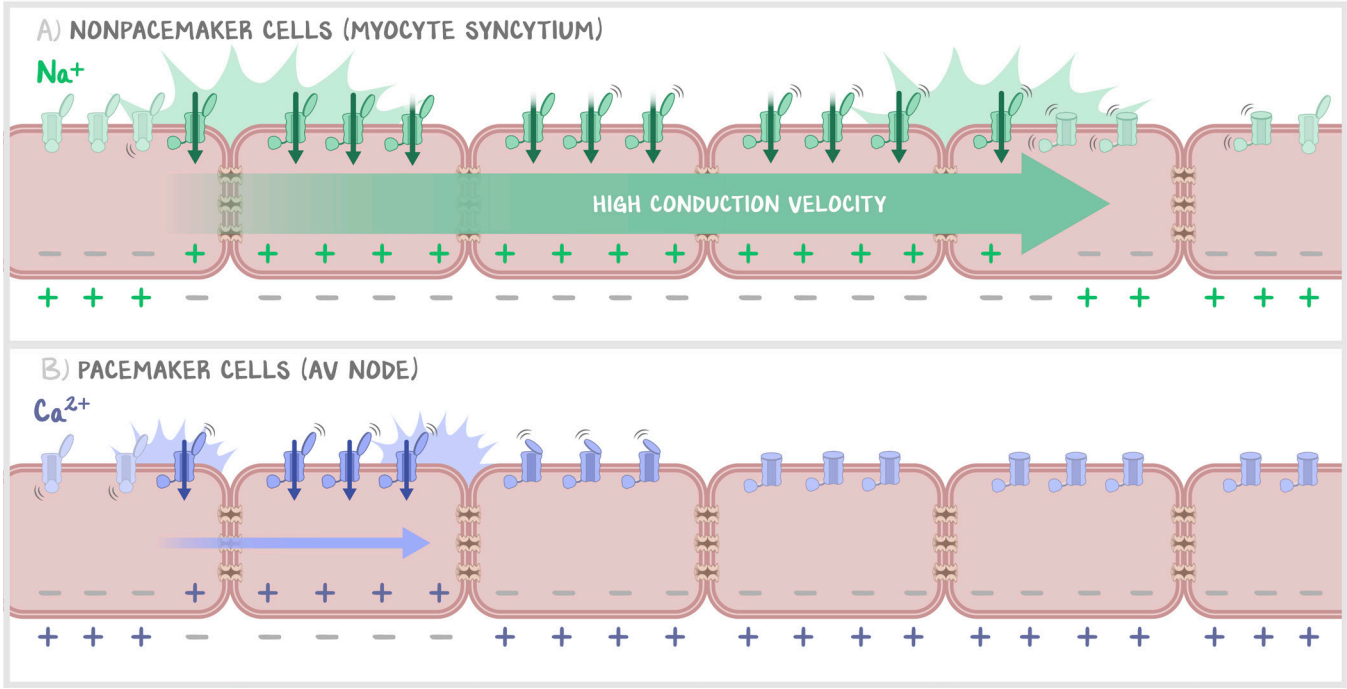

Figure 2.2: Conduction Velocity
(a) A larger depolarizing stimulus is effectively communicated through gap junctions to more myocytes farther away. In turn, they propagate that signal, depolarizing still farther myocytes. When Sodium and Calcium Channels are available, conduction velocity is high (within atrial or ventricular syncytia). (b) A smaller depolarizing stimulus is communicated through gap junctions to fewer myocytes close by. In turn, they propagate that signal, depolarizing only nearby myocytes. When Sodium Channels are absent, and the only channels are for calcium, the conduction velocity is low (the AV node).

The idea is that pacemakers have a modest depolarization but also possess automaticity. Nonpacemaker myocytes don't possess automaticity but make sure the pacemaker depolarization is heard loud and clear. The pacemakers set the heart rate, depolarizing the nearby nonpacemakers. The nonpacemakers' depolarization is large, loud, and mediated through Sodium Channels. This ensures that all the myocytes of each syncytium depolarize together. The conduction velocity is fast. But because there is a separation of the atrial syncytium and the ventricular syncytium, there must be something that prevents the conduction of the atrial nonpacemaker signal to the ventricular nonpacemakers. That is both the fibrous ring that prevents the conduction of the electrical signal and the AV node. The AV node has only pacemakers. The benefit here isn't that they make a pace. The benefit here is that because these pacemakers have only calcium channels and no sodium channels, and calcium isn't as loud a signal as sodium, the conduction velocity is slow through the AV node.

Timing of Conduction

The atria depolarize and subsequently contract from the top down—the direction they want the blood to go. The ventricles depolarize and subsequently contract from the bottom up—the direction they want the blood to go. The timing of contraction is dependent on the arrangement of the conduction fibers. The SA node is on top, the AV node separates the atria from the ventricles, and the fibers run through the interventricular septum to the apex, then up and around the ventricles.

An action potential is initiated at the sinoatrial node (the **SA node**) in the posterior of the right atrium. From there, the action potential is propagated by the cardiac myocytes, acting as a syncytium, connected to one another by gap junctions. There are no specific fibers in the atria that carry the signal—the syncytium is the structure that conducts the action potential. The cells nearest the SA node depolarize first, then the

signal propagates forward and around the atrial syncytium. The signal propagates quickly through all atrial myocytes. When the signal runs into the atrioventricular septum, the signal stops—the atrial myocytes behind the direction of propagation are refractory (so cannot depolarize), and the atrioventricular septum is a fibrous (nonconducting) tissue that separates the atrial syncytium from the ventricular syncytium.

The time of depolarization rushes rapidly through the atrial syncytium, from the top (SA node) to the base (the atrioventricular septum). Contraction follows depolarization in the same order. The top of the atria contracts first, then the contraction travels down the sides, maximizing contractile force towards the ventricles, through the atrioventricular valves. That depolarization signal is rapidly conducted to the AV node by interatrial fibers. When the depolarization signal arrives at the AV node, the atrial contraction has not even started yet. The AV node has a slow conduction velocity. The signal creeps slowly through the AV node into the bundle of His. Atrial contraction begins. As the signal finally drags itself out of the AV node, it hits the ventricular syncytium. Depolarization travels rapidly again.

The conduction system is arranged so that the interventricular septum, between the two ventricles, channels two signals, one to the right, one to the left. The atria were smaller and could rely on the syncytium to coordinate the depolarization. The ventricles are bigger. The signal is coming from the atria, from above. The best orientation to eject blood up and out through the semilunar valves is to start at the bottom of the heart and squeeze the blood up. The contraction should start at the bottom, then continue sequentially up towards the valves. That means the electrical signal should start at the bottom of both ventricles and travel up the sides of both ventricles at the same time.

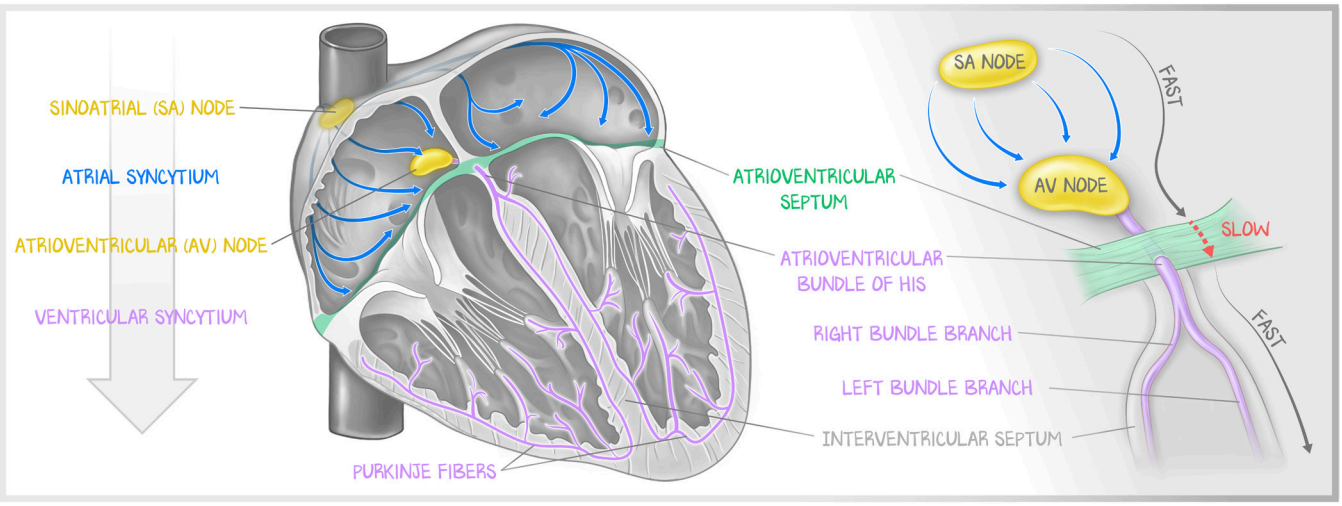

Figure 2.3: Conduction Anatomy
The sequence of depolarization is well defined and follows the SA node down through the Purkinje fibers. There is a conduction delay through the AV node, attributable to the specialized conduction system across the fibrous atrioventricular septum.

There is a connection between syncytia, but only at the **AV node**. As the signal enters the AV node, it begins to travel very slowly through the AV node and below the atrioventricular septum. This delay enables the atria to contract (depolarization happens far faster than contraction), delivering the last bit of preload (called the atrial kick) that adds a little more stretch to the cardiac myocytes' sarcomeres, better maximizing their sarcomere length, generating a higher stroke volume. After the signal exits the AV node, it is carried in the **bundle of His**. The bundle of His arises in the interventricular septum and immediately bifurcates into the **right bundle branch** and **left bundle branch**. Both bundle branches run down toward the apex within the **interventricular septum**. These are true tracks of conducting myocytes in the **subendocardial connective tissue**. They terminate in **Purkinje fibers**, first descending to their respective ventricular apex, then ascending from their ventricle's apex back up along the lateral wall.

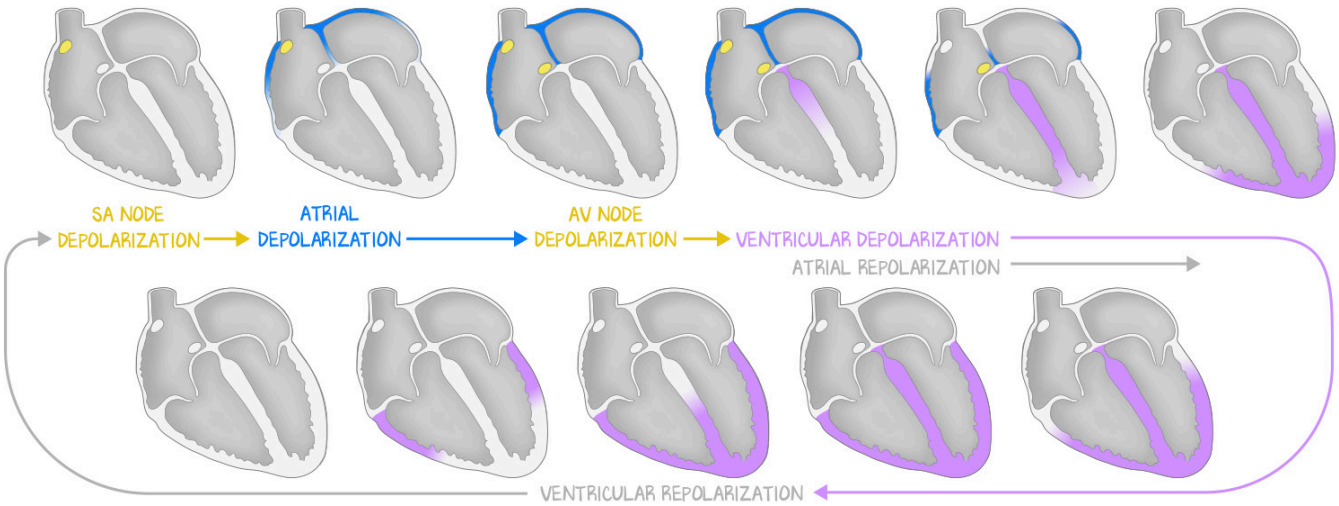

Figure 2.4: Normal Conduction
This is the path of depolarization and repolarization of the myocardium. It demonsatrates directionality and what tissue is doing what—repolarizing, depolarizing, resting—in which order. What is not depicted is speed. The atria (blue) depolarize very quickly. The signal reaches the AV node, and pauses. The signal is then sent down the interventricular septum to the apex, and then back up the sides of the heart. The SA node, entirety of the atria, and the AV node hear the depolarizing signal almost at the exact same time. The only path through the atrioventricular septum is the AV node into the Bundle of His, and down the right and left bundles of the interventricular septum.

Ventricular Myocyte Action Potential: Nonpacemakers

The cardiac action potential is broken into four phases, each dominated by a particular current. Nonpacemakers use Sodium Channels, Calcium Channels, Potassium Channels, and the channels that enable this thing but we don't want you paying attention to—I_{TO}. Phase 0 (depolarization) is caused by Sodium Channels. Phase 1 (initial repolarization) is caused by Potassium Channels. Phase 2 (plateau) is caused by Calcium Channels. Phase 3 is caused by Potassium Channels. Phase 4 (rest) is caused by potassium leak channels as in all excitable cells. That's what you should learn cold.

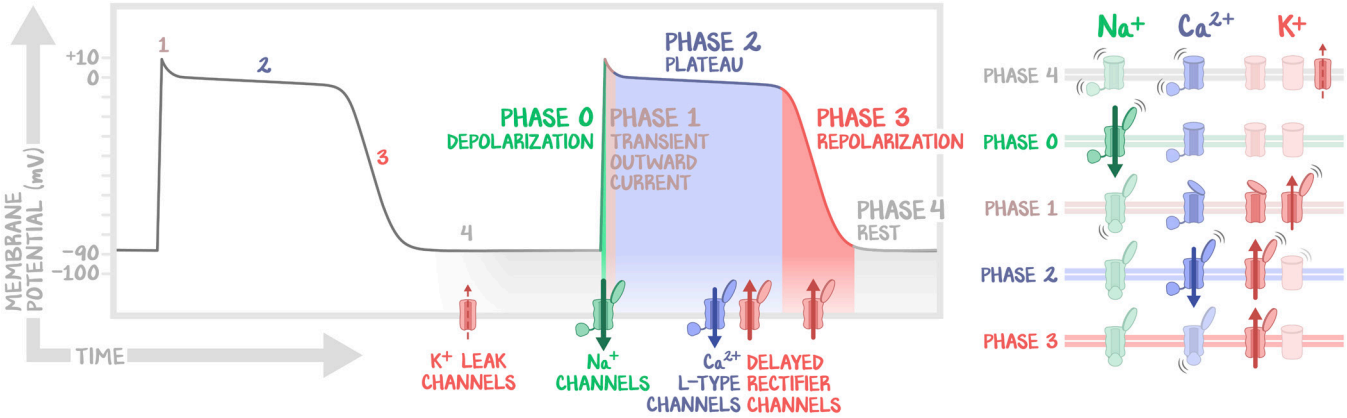

Figure 2.5: Myocyte Action Potential

Phase 4 is the resting membrane potential. The **resting membrane potential** of a nonpacemaker is approximately –90 mV. At rest, there is permeability only to potassium. The Na^+-K^+-ATPase establishes a favorable concentration for K^+ to leave the cell. Leak currents allow for K^+ to efflux from the cell, driving the cell towards the equilibrium potential for K^+, approximately –90 mV.

Phase 0 (depolarization). *Sodium Channels open, Calcium Channels are opening, and fast Potassium Channels (ITO) open. Slow Potassium Channels also start to open*. A **depolarization** (carried from one cell to the next through gap junctions) reaches the myocyte. All of the channels receive the same signal to open—depolarization. All the channels open. The Sodium Channels are the fastest to open and create the largest conductance to any ion. The membrane potential, being dominated by massive sodium conductance, goes towards the equilibrium potential for sodium. The cell depolarizes. The other channels are opening, but sodium channels are open.

Phase 1 (initial repolarization). *Sodium Channels inactivate.* The Sodium Channels rapidly inactivate. The cell membrane conductance to Na^+ goes to zero, and there is no sodium-driven force to depolarize the cell. The Calcium Channels are open, so there is now some depolarizing signal through those channels. The I_{TO} channels remain open. The closure of the Sodium Channels and the still-open potassium channels causes the short hyperpolarization. At the end of phase 1, the rapid-open potassium channels inactivate. Now, only Calcium Channels and Potassium Channels are open.

Phase 2 (plateau). *Calcium Channels remain open, Potassium Channels remain open, and the flow of calcium is balanced to the flow of potassium.* The Sodium Channels were inactivated by the end of phase 0. The I_{TO} channels were inactivated by the end of phase 1. Now, in phase 2, the Calcium Channels are open and will eventually inactivate. Potassium Channels are now also open, and they will never inactivate (they will close with hyperpolarization and time but have no inactivation gate). The efflux of K^+ matches the influx of Ca^{2+}. There is no net change in voltage; thus, there is a plateau. At the end of phase 2, the Calcium Channels inactivate. Because the Potassium Channels never inactivate, the time the Calcium Channels remain open determines the **duration of the plateau** and, therefore, the **duration of the action potential**.

Phase 3 (rapid repolarization). *Calcium Channels inactivate, and Potassium Channels remain open.* All of the Calcium Channels opened at about the same time, much like Sodium Channels do. All of those Calcium Channels will inactivate at about the same time as well, just like Sodium Channels do. And the change will be just as abrupt. It's just that Calcium Channels open a little slower, and it takes a **lot longer** for the Calcium Channels to inactivate. With the membrane conductance to any depolarizing signal terminated (Sodium Channels inactivated at the end of phase 1, Calcium Channels inactivated at the end of phase 2), and the membrane conductance of K^+ remaining massively high, the cell hyperpolarizes.

Phase 4 is the **resting membrane potential**. Atrial and ventricular myocytes, non-nodal nonpacemaker cells, have a very negative resting potential (–90 mV). With enough time and hyperpolarization, the activation gate closes on all channels. For those with an inactivation gate, that is accompanied by the inactivation gates opening. All channels go back to the resting state, ready to be opened again, at about the same time.

Nodal Action Potentials: Pacemaker

The **pacemaker myocytes** have a much simpler action potential, as they lack phases 1 and 2. This means pacemakers **lack Sodium Channels (I_{Na}) and I_{TO} channels**. The pacemakers do not go to –90 mV, and they don't have a flat resting membrane potential because they **have Funny Channels** (I_F). Their purpose is to determine the heart rate (I_F) and delay conduction velocity (absence of I_{Na}). They do use the same Calcium Channels and Potassium Channels as nonpacemakers.

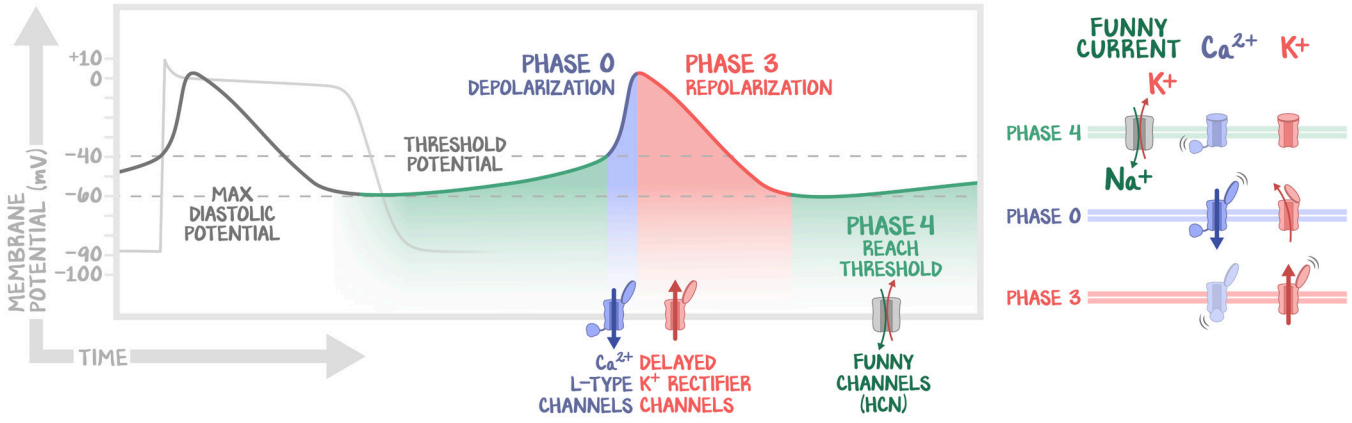

Figure 2.6: Pacemaker vs. Myocyte Action Potentials
Pacemakers use only Calcium Channels, Potassium Channels, and Funny Channels. Their phase 4 has a slope, and their phase 0 is more gradual.

Phase 0: *Calcium Channels (ICa) open, and Potassium Channels (IK) open but slower than Calcium Channels.* A depolarization arrives at the pacemaker. Calcium Channels open. Calcium Channels lead to a modest depolarization. Therefore, the I_{Ca} phase 0 will show a less brisk upstroke and not reach nearly the same voltage as the I_{Na} phase 0 of nonpacemakers. This slow increase and modest elevation are what will make the pacemakers capable of delaying conduction through the AV nodes.

Phase 1. N/A

Phase 2. N/A

Phase 3. *Calcium Channels (ICa) close, Potassium Channels (IK) remain open.* As Calcium Channels inactivate, dropping the conductance to calcium while the Potassium Channels remain open, I_K drives the cell towards the resting membrane potential. If these were nonpacemakers, that would mean toward a resting membrane potential of –90 mV. But that doesn't happen in pacemakers. Instead, the Potassium Channels drop the pacemaker to maximum diastolic potential. **Maximum diastolic potential** is the physiology term for the most negative the pacemaker gets—not how high the action potential is. We like to think about it as the minimum diastolic potential, as it is the lowest the tracing goes on the graph. But there is no physiology term for minimum diastolic potential, so you can't be confused. They are both the same thing.

Phase 4. *Funny Channels (IF) "open," slowly depolarizing the pacemaker.* There is **no resting membrane potential** for pacemakers. At the end of the action potential, the Potassium Channels drive the pacemaker to the maximum diastolic potential, the lowest voltage the cell will get to. That voltage is around –60 mV, which is far more positive than the –90 mV of nonpacemakers. The Funny Channels give phase 4 a slope, allowing for automaticity.

Linking Channels to Depolarization in Pacemakers

Automaticity is built into pacemakers by having a maximum diastolic potential near the threshold and a current that slowly depolarizes the cell toward the threshold without any stimulus other than the channel itself. The frequency of depolarizations determines the heart rate. Depolarization is about **reaching the threshold** (approximately –40 mV). The rate at which a pacemaker reaches threshold is dependent on the starting point—the **maximum diastolic potential** (the lowest the potential goes during Phase 3)—the endpoint—**threshold potential** (the threshold at which phase 0 initiates)—and how fast it can get from start to end—the **slope of phase 4** (changing membrane conductance to the I_F).

The **slope of phase 4** is all about **Funny Channels**. The more Funny Channels there are, the faster the depolarization and the steeper the slope. And of course, the inverse—the fewer Funny Channels, the lower the permeability to the Funny Current and the longer it would take to reach the threshold.

The **maximum diastolic potential** is all about **Potassium Channels**. The more Potassium Channels there are, the more that are open, the closer the cell will get to the equilibrium potential for potassium, the more negative it will become. Because pacemakers never reach the equilibrium potential for potassium as nonpacemakers do, adding more Potassium Channels will continue to cause the maximum diastolic potential to approach the equilibrium pressure for potassium. The lower phase 4 starts, the longer it will take to reach the threshold.

Threshold potential is all about **Calcium Channels**—how many are closed and ready to open. The fewer calcium channels ready to open, the higher threshold will be. Think back to the discussion of absolute and relative refractory periods in General Physiology. A second action potential could be generated with a higher stimulus during the relative refractory period because there were some, but not all, Sodium Channels ready to open. This is analogous to Calcium Channels here. More of them ready to open means more like normal, with a threshold potential of –40 mV. Fewer of them ready to open means more stimulus will be needed, increasing the threshold potential (Figure 2.7c).

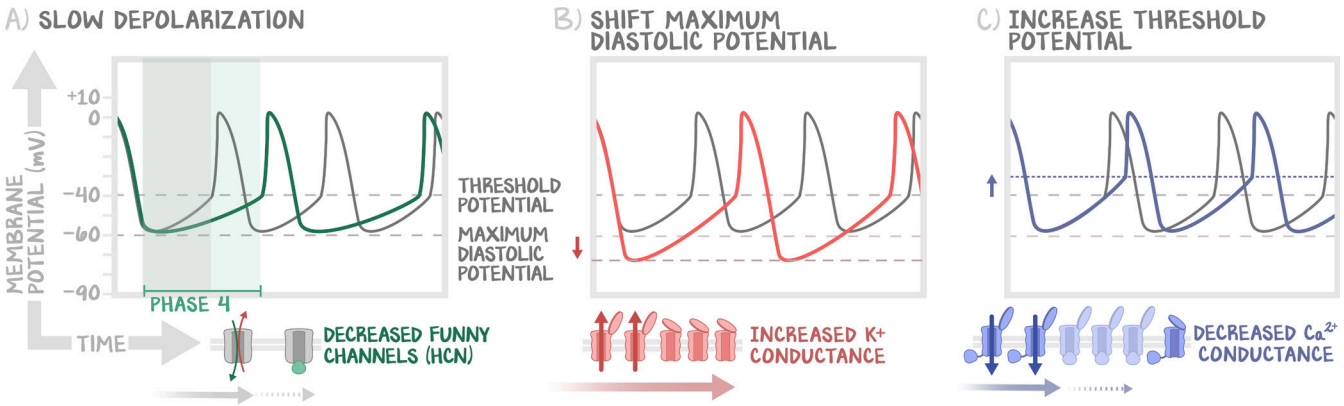

Figure 2.7: Rate Control Methods
(a) By inhibiting the Funny Current, the slope can be made smaller, so more time is required to reach the threshold, slowing the heart rate. (b) By increasing the cell membrane conductance to potassium, the starting diastolic potential will be lower, and so it will take more time to reach the threshold. (c) By inhibiting the Calcium Channels, by increasing the threshold potential, the distance phase 4 will travel is increased, taking more time to get to the threshold.

We can use pharmacology to manipulate this system. Our autonomic nervous system manipulates it, too.

Autonomic Mechanisms of Rate Control

The second messenger pathway involves the use of G protein-coupled receptors. Every organ, every module has second messengers. This system was how we explained physiological antagonism—the sympathetic nervous system stimulates the heart while the parasympathetic nervous system pauses the heart. They have completely different receptors and different G proteins coupled to their receptor. One G protein is G_s, which stimulates adenylyl cyclase. The other G protein is G_i, which inhibits adenylyl cyclase. Adenylyl cyclase transforms ATP to cAMP. As cAMP levels rise (G_s), there are both immediate effects in phosphorylation states (enacted through protein kinase A; PKA) and longer-term effects enacted by gene transcription because of cAMP response element-binding (CREB). Which phosphorylation state does what for each voltage-gated channel is beyond the scope of this course.

Sympathetics stimulate by increasing cAMP, parasympathetics pause by decreasing cAMP.

Parasympathetics release acetylcholine at their synapse with **nodal tissue**. Parasympathetics do not innervate the ventricles. The result of **M_2 receptor activation** is more Potassium Channels, fewer Calcium Channels, and fewer Funny Channels. "Fewer" means fewer ready to open in the plasma membrane—whether it be an actual number or phosphorylation state is irrelevant. The conductance to calcium decreases, increasing the depolarization threshold. The conductance to the Funny Current goes down, decreasing the slope of phase 4. The conductance to potassium goes up, making the maximum diastolic potential more negative. **All three slow the heart rate** and **decrease conduction velocity** through the AV node.

Sympathetics release norepinephrine at their synapses with **nodal tissue** and **ventricles**. Sympathetics do innervate the ventricles, which is how contractility was increased and myocardial work went up in the Structure and Function island. The result leads to the opposite of the parasympathetics—fewer Potassium Channels, more Calcium Channels, and more Funny Channels. Sympathetics provoke a less negative maximum diastolic potential, a steeper slope of phase 4, and a lower threshold potential, all of which **increase heart rate**.

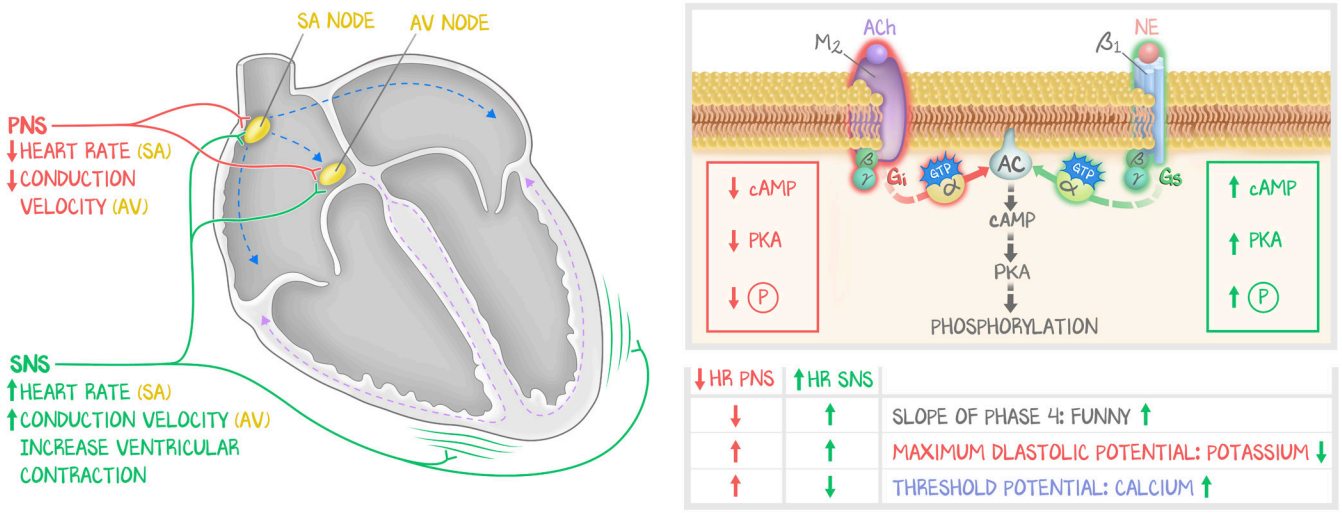

Figure 2.8: Autonomic Control
(a) Sympathetics innervate both the nodes and ventricles, increasing heart rate, increasing conduction velocity, and increasing ventricular contraction. The parasympathetics innervate the nodes only, decreasing heart rate and decreasing conduction velocity. (b) Parasympathetics exert their effects via the vagus nerve, release of acetylcholine, and activation of G_i-coupled receptors. Sympathetics exert their effects via the sympathetic chain, using norepinephrine to activate β_1 receptors, which activates G_s-coupled receptors.